

Production of co-amorphous materials with therapeutic activity

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Introduction: Orally administered drugs must have sufficient water solubility to ensure that they are absorbed in the gut, as required for bioavailability and therapeutic activity. As the number of poorly water soluble drug molecules entering the clinic rises, the strategies to enhance solubility also become increasingly important. Conversion of a crystalline drug into the amorphous form is one way to improve its apparent solubility and dissolution rate (a measure of bioavailability). Unfortunately, the large internal energy and molecular movement of the molecules in the amorphous state may also cause the material to convert spontaneously back to its stable crystalline form during processing, storage or dissolution (1,2). Co-amorphous structures containing one, or more, small molecular weight compounds, which are homogeneously mixed to form a new entity with a single amorphous phase (2,3), have been shown to stabilize the amorphous form of a drug in the solid state (2). Finding low molecular weight excipients compatible with the model drug may, however, be challenging (3). In this respect, amino acids have proved their potential to form co-amorphous systems with some drugs and are the object of the present work (1,2). Different techniques are available to obtain co-amorphous systems, namely ball milling or quench cooling, since these techniques inflict limited chemical degradation to the drug (1,2).

Materials and Methods: Mixtures of olanzapine and L-arginine and L-tryptophan (1:1) and paroxetine or gabapentin and L-arginine, L-tryptophan, L-proline, L-lysine, L-tyrosine and L-phenylalanine (1:1) were processed by ball milling and quench cooling. The new products were characterized by Differential Scanning Calorimetry (DSC) in order to identify the formation of co-amorphous between each drug and the amino acid.

Results: Results have shown that olanzapine could not be converted into the amorphous state in combination with arginine or tryptophan, either by ball milling, or quench cooling. Similarly, gabapentin did not convert into the amorphous state neither by ball milling, nor by quench cooling. Interestingly, olanzapine became amorphous only by quench cooling, whereas paroxetine became amorphous by both ball milling and quench cooling. In turn, paroxetine was converted into the amorphous form when in combination with the amino acid L-proline.

Discussion and Conclusions: The study has shown that the conversion of crystalline drugs into the amorphous state is dependent on their chemical structures and interactions with other chemical entities. For the model drugs studied the use of specific amino acids, in combination with the appropriate processing technique, has confirmed the potential to form co-amorphous systems. The use of amino acids thus indeed seem to be a promising approach, provided the right combination (drug:amino acid) and processing technique have been identified.

References:

1. Lobmann K., Grohganz, H., Laitinen, R., Strachan, C., & Rades, T. Amino acids as co-amorphous stabilizers for poorly water soluble drugs - Part 1: Preparation, stability and dissolution enhancement. *Eur J Pharm Biopharm.* 2013; 85: 873-81.
2. Dengale, S. J., Grohganz, H., Rades, T., & Löbmann, K. Recent advances in co-amorphous drug formulations. *Adv Drug Deliv Rev.* 2016; 100: 116-25.
3. Jensen, K. T., Larsen, F. H., Löbmann, K., Rades, T., & Grohganz, H. Influence of variation in molar ratio on co-amorphous drug-amino acid systems. *Eur J Pharm Biopharm.* 2016; 107: 32-9.

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